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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/832,818	04/12/2001	Pnina Fishman	2786-0170P	1935

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EXAMINER	
YOUNG, JOSEPHINE	

ART UNIT	PAPER NUMBER
1623	11

DATE MAILED: 01/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/832,818	FISHMAN, PNINA	
	Examiner	Art Unit	
	Josephine Young	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence addr ss --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 November 2002 and 23 December 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *17-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16 and 27-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,5,6* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of the invention elected in Paper No. 8, of November 8, 2002, is acknowledged. The traversal is on the ground(s) that the inventions of Groups I and II share the same mode of operation and the same effect. This is not found persuasive because while the effect of the methods may be the same, the methods of Groups I and II have different modes of operation, and thus are not related. The method of Group I involves the administration of compound(s), while the method of Group II involves the administration of activated natural killer cells. The method of one does not render obvious the method of the other. As set forth in the Office Action of October 10, 2202, searches for the two groups would not be co-extensive. Further, searching both the inventions constitutes a burdensome search, as a thorough search comprises a search of foreign patents and non-patent literature, as well as the appropriate U.S. patent classifications. To search the two independent and distinct inventions, would indeed impose an undue burden upon the Examiner in charge of this application.

The requirement is still deemed proper and is therefore made FINAL.

Accordingly, claims 17-26 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Further, Applicant's election of species in Paper No. 10, of December 23, 2002, is acknowledged. As Applicant did not indicate that the election is traversed, and because

Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Specification

The disclosure is objected to because of the following informalities: On page 13, lines 7-8, the specification refers to Cl-IB-MECA as 2-chloro-N^6-(3-iodobenzyl)-adenosine-5'-N-methyl-uronamide. However, throughout the rest of the specification, Cl-IB-MECA is referred to as 2-chloro-N^6-(2-iodobenzyl)-adenosine-5'-N-methyl-uronamide (Cl-IB-MECA).

Appropriate correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Undue experimentation is a conclusion reached by weighing the noted factual considerations set forth below in In re Wands USPQ2d 14000. A conclusion of lack of enablement means that, based on the evidence regarding a fair evaluation of an appropriate combination of the factors below, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention.

These factors include

(1) quantity of experimentation necessary,

(2) the amount of guidance presented,

(3) the presence or absence of working examples,

(4) the nature of the invention,

(5) the state of the prior art,

(6) the predictability of the art and

(7) the breath of the claims.

Claims 1-16 and 27-35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods to activate natural killer cells using 2-chloro-N^6-(2-iodobenzyl)-adenosine-5'-N-methyl-uronamide (Cl-IB-MECA), does not reasonably provide enablement for methods to activate natural killer cells using any other adenosine A3 receptor agonist. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

With regard to factors (1) and (2) cited above, undue experimentation is required to determine which adenosine A3 receptor agonist, and at what concentrations and specificity, would be effective for activating natural killer cells for which the instant invention is applicable. There has not been provided adequate guidance in the written description for accomplishing and determining such, as only one particular agonist was tested, out of the numerous variants that are included in the generic formulas.

With regard to factors (4), (5) and (6), it is noted that there is a great deal of unpredictability in the art. For example, WILLIAMS *et al.*, Experimental Cell Research, **1997**,

233, 187-197 (W), teaches that N^6-[2-(4-aminophenyl)ethyl]adenosine (APNEA), an adenosine A_1/A_3 agonist, failed, at the concentrations tested (0.1-5 μM and 10 μM), to induce BLT esterase secretion by NK cells. See page 190, right column, lines 1-4. Therefore, the art at the time the invention was made fails to establish predictability with regard to the properties of the compounds that fall within the generic formula needed to perform the scope of the methods as instantly claimed.

With regard to factors (3) and (7), it is noted that while there is one working example, it is not seen as sufficient to support the breath of the claims. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves. See In re Gardner et al. 166 USPQ 138 (CCPA 1970).

Further, claims 9-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods to activate natural killer cells using 2-chloro-N^6-(2-iodobenzyl)-adenosine-5'-N-methyl-uronamide (Cl-IB-MECA), hence enabling for methods to treat various tumor cells in which natural killer cells are known to one of ordinary skill in the art to be cytotoxic, does not reasonably provide enablement for methods for a therapeutic treatment of any other disease or symptom of a disease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

With regard to factors (1) and (2) cited above, undue experimentation is required to determine which disease and/or symptom of disease, would be effected by activation of natural

killer cells for which the instant invention is applicable. There has not been provided adequate guidance in the written description for accomplishing and determining such, as no assay and/or animal model was described to assess which disease or symptom of disease would be effected by activation of natural killer cells and/or a particular adenosine A3 receptor agonist, out of the numerous diseases or symptoms of diseases that can be implicated in the activation of natural killer cells.

With regard to factors (4), (5) and (6), it is noted that there is a great deal of unpredictability in the art. For example, within the art specifically pertaining to cancer therapeutics, while certain agents and compositions are known to treat certain forms of cancer, no effective agent or composition has been found for the treatment of all cancer types. Therefore, the art at the time the invention was made fails to establish predictability with regard to the properties of the disease or symptom of disease that fall within the generic formula needed to perform the scope of the methods as instantly claimed.

With regard to factors (3) and (7), it is noted that while there is one working example of activation of natural killer cells, it is not seen as sufficient to support the breath of the claims. It is noted that Law requires that the disclosure of an application shall inform those skilled in the art how to use applicant's alleged discovery, not how to find out how to use it for themselves. See In re Gardner et al. 166 USPQ 138 (CCPA 1970).

Claim Rejections - 35 USC § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-16 and 28 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "individual" in claims 1-16 renders the claims in which it appears indefinite. It is unclear as to if an individual is limited to humans, mammals, animals and/or cells.

The phrase "sulfur of carbon atom" in claims 2, 10 and 28 renders the claims in which it appears indefinite. It is unclear as to if Applicant meant "sulfur or carbon atom." Further, it is unclear as to how Y can simply be a carbon atom, as that would imply a bivalent carbon.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by WILLIAMS (W).

WILLIAMS teaches that 2-chloroadenosine, an adenosine receptor agonist, stimulates natural killer cells. See Abstract.

Claims 27-35 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by patent US 5,773,423 to JACOBSON et al (A).

JACOBSON teaches the adenosine A3 agonists of the present invention. See col. 6, lines 1-35. In col. 19, line 29 to col. 21, line 52, JACOBSON discloses the various pharmaceutical formulations of the present invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over WILLIAMS (W) and JACOBSON (A).

Applicant claims methods to activate natural killer cells and methods for therapeutic treatment through activation of natural killer cells via an adenosine A3 receptor agonist. In particular, Applicant claims methods via an agonist of formula (I) or (IV), and in particular N^6-[2-(4-aminophenyl)ethyl]adenosine (APNEA), N^6-(4-amino-3-iodobenzyl)-adenosine-5'-N-

methyl-uronamide (AB-MECA), N^6-(2-iodobenzyl)-adenosine-5'-N-methyl-uronamide (IB-MECA) or 2-chloro-N^6-(2-iodobenzyl)-adenosine-5'-N-methyl-uronamide (Cl-IB-MECA).

WILLIAMS teaches that 2-chloroadenosine, an adenosine receptor agonist, activates natural killer cells, as exhibited by increased BLT activity. See Abstract.

WILLIAMS does not specifically disclose that the N^6-(2-iodobenzyl)-5'-N-methyl-uronamide derivative of 2-chloroadenosine, nor any other adenosine A3 receptor agonist, would activate natural killer cells.

JACOBSON teaches that modification of the adenosine at the 5'-position and/or at the N^6-position will moderate A_3 selectivity. See col. 2, lines 64-66. In particular, in col. 2, line 67-col. 3, line 7, JACOBSON discloses that the 5'-methyluronamide modification of adenosine and the N^6-benzyl group, either alone or in combination, increases affinity in binding to A_3 receptors. For example, N^6-(2-iodobenzyl)-adenosine-5'-N-methyl-uronamide (IB-MECA) is 50-fold more selective for A_3 versus either A_1 or A_2 receptors.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the 2-chloroadenosine of WILLIAMS to enhance the activation of natural killer cells. A skilled artisan would have been motivated and had a reasonable expectation of success to derivatize 2-chloroadenosine with 5'-methyluronamide and the N^6-benzyl group, either alone or in combination, to increase the affinity in binding to A_3 receptors, as per JACOBSON.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Related Prior Art

PRIEBE *et al.*, Cancer Research, **July 15, 1990**, *50*, 4328-4331 (U) and PRIEBE *et al.*, Cancer Research, **September 1, 1988**, *48*, 4799-4803 (V) teach that modulation of natural killer cells can be achieved via the adenosine A_1 or A_2 receptor. While, neither reference specifically implicates the adenosine A_3 receptor in the activation of natural killer cells, both references teach that adenosine receptors in general are involved in the activation of natural killer cells.

Conclusion

Claims 1-35 are pending. Claims 17-26 are withdrawn. Claims 1-16 and 27-35 are rejected. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Josephine Young whose telephone number is (703) 605-1201. The examiner can normally be reached on Monday through Friday, 9:00 a.m. to 6:00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached at (703) 308-4624. The fax phone numbers for the

organization where this application or proceeding is assigned are (703) 305-3014 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

JY
January 27, 2003

JAMES O. WILSON
SUPERVISORY PATENT EXAMINER
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